Original Article

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Critical Evaluation of various Sonologic Parameters of Early Foetal Growth Discrepancies in Predicting Adverse Pregnancy Outcomes

Obstetrics and Gynaecology Section

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ABSTRACT

Introduction: It is well established that adverse perinatal outcomes such as Small for Gestational Age (SGA), preterm delivery, and pre-eclampsia are associated with higher incidence of neonatal complications and death. Evidence suggests that these adverse outcomes may have their origins dating back to early pregnancy growth discrepancies.

Aim: To establish an association between early fetal growth discrepancies and occurrence of adverse obstetric outcomes such as pre-eclampsia and SGA.

Materials and Methods: This is a prospective observational study done in the Department of Obstetrics and Gynaecology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India, between Jan 2015 to May 2016 involving 314 pregnant women, using Crown Rump Length (CRL) measurements at the time of early anomaly (11-14 week scan). Pregnancies with congenital and chromosomal defects, multifetal gestation and non viable foetuses were excluded from the study. The biometric parameters mainly Biparietal Diameter (BPD), Head Circumference (HC), Abdominal Circumference (AC), Femur Length (FL), and Estimated Foetal Weight (EFW) at the time of targeted organ scan (between 18 to 20 weeks) were recorded and reverse calculations were done to convert these parameters to corresponding GA based on published regression formulae. The GA at the time of targeted scan was also calculated based upon the first trimester CRL values. The growth discrepancy was calculated by deducting CRL based GA from biometrically estimated GA for each individual growth parameters. Fisher's-exact test was used to compare the means of biometric lags in SGA vs. Appropriate for Gestational Age (AGA) fetuses and also in Pre-eclampsia vs. normotensive groups. For each biometric parameter, the best cut-off for discrepancy value was determined using Receiver Operator Characteristic (ROC) analysis along with their diagnostic ability to predict occurrence of SGA in terms of sensitivity, specificity, positive and negative likelihood ratio with their 95% confidence intervals. The Area Under Curve (AUC) and z-test statistics were taken into account to decide the best parameter to predict adverse outcome. A p-value of <0.05 was considered statistically significant.

Results: Out of 314 women studied, 62 (19.7%) delivered an SGA neonate, and 30 (9.5%) had pre-eclampsia. All biometric parameters of SGA babies showed growth lag compared to AGA babies which was statistically significant (BPD $p<0.001$, HC $p<0.001$, AC $p<0.001$, FL $p<0.01$, and EFW $p<0.001$). However, we could not establish similar associations between early growth discrepancies and onset of pre-eclampsia.

Conclusion: Models of second trimester growth discrepancies can be used to predict SGA babies. Earlier anticipation of adverse perinatal outcome may add to quality of antenatal care and timely delivery to prevent late stillbirths associated with SGA.

Keywords: Early growth discrepancy, Foetal biometry, Pre-eclampsia, Small for gestational age

INTRODUCTION

It has been previously thought that foetal growth remains similar irrespective of ethnicity, socioeconomic status, multifoetal gestation etc., up to the end of second trimester of pregnancy [1]. This hypothesis was challenged when technical advances in ultrasound examination made estimation of various biometric parameters in the early part of the pregnancy which included parameters such as CRL, BPD, HC, AC and FL [2,3].

Birth of a SGA neonate brings anxiety to parents, obstetrician, as well as to the neonatologist as it is well known that low birth weight due to SGA is associated with short and long term child development issues and carrying its effect to the late adulthood with increased risk of cardiovascular and metabolic dysfunction such as diabetes [4-9]. In addition, placental insufficiency in the early pregnancy may be associated with risk of development of pre-eclampsia [10-12].

Now, it is very well established that a discrepancy in BPD growth between 11 to 20 weeks is associated with adverse maternal foetal neonatal outcomes such as low birth weight, prematurity, increased risk of still birth [13]. Hypertensive disorders of pregnancy, preterm delivery, decreased foetal size are also found be associated with first trimester growth discrepancies [14]. Even the foetal weight discrepancy below the 25th centile between fourth and sixth month of gestation has translated to increased prevalence of small babies, prematurity, pre-eclampsia and perinatal morbidity and mortality [15]. There are only few studies available on this topic, but all are reported from western countries. There is no such study reported from India so far. Therefore, we feel that the findings of the present study can be shared among obstetricians and measures may be taken to reduce neonatal morbidity or morality. Keeping this point in view, the present study was conducted with an aim to establish an association between early fetal growth discrepancies and occurrence of adverse obstetric outcomes such as pre-eclampsia and SGA.

MATERIALS AND METHODS

This is a prospective observational study done in the Department of Obstetrics and Gynaecology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India, between Jan 2015 to May 2016 involving 314 pregnant women. The institutional regulatory body gave the permission to conduct the study. Informed consent was taken from the participating women and study protocol followed ethical code of declaration of Helsinki.

All of these women underwent early anomaly scan at 11-14 weeks and GA was reassigned based on CRL measurements. Pregnancies with congenital and chromosomal defects, multifoetal gestation and non viable foetuses were excluded from the study. The ultrasound examinations were again repeated between 18-20 weeks and important biometric parameters (BPD, HC, AC, FL and EFW) were recorded for further analysis. The pregnancies were followed up till the time of delivery and adverse outcomes were tabulated.

The main emphasis was to establish the correct dating of pregnancy as accurate estimation of GA was mandatory to correctly time the growth delay. The CRL measured at first visit of importance (11-14 weeks) and CRL based corrected GA was taken into account for further calculations [Table/Fig-1] [16]. In the subsequent visit for targeted scan (between 18-20 weeks), the other parameters such as BPD, HC, AC, FL, EFW, including CRL were obtained in a routine manner, as these measurements are integral part of standard ultrasound examination. Each of these parameters was converted to corresponding GA using published equations (BPD, HC, AC, FL and EFW) as shown in [Table/Fig-1] [17-21]. As most computer programs in ultrasound machine calculate EFW based on BPD, HC, AC and FL, GA was expressed directly as a function of these parameters using well established Hadlock formula [21].

The growth variation at two different period of time was calculated using the method as described by Schwartz N et al., [22]. Having two scans at two different instances, once between 11 to 14 weeks and the second one at the time of anomaly scan (18 to 20 weeks) helped us to calculate the time elapsed (in days) between two scans and this period was added to the GA obtained at the first scan to calculate the exact GA of the foetus at the time of second scan. Using the biometric parameters obtained during the second scan and referring to GA formulae, the ultrasound estimated GA was also calculated at the same time [Table/Fig-1]. The difference between actual GA and the ultrasound estimated GA was considered to be growth discrepancy. For example, the difference was "0", then it is considered as the foetus is growing at appropriate velocity, if the difference is a positive integer, then it equated to accelerated growth and similarly if the difference was negative integer, the foetus was designated to have growth discrepancy. These growth discrepancies were calculated for each of above mentioned biometric parameters and were entered into database with their exact sign values. The [Table/Fig-2] shows some illustrations of these steps for different cases and different parameters. By considering the early CRL measurement for GA estimation, the inaccuracies associated with dating based on last menstrual period is thus avoided.

Biometric variables	Regression formula
CRL	$GA=40.9041+3.21585\times CRL^{0.5}+0.348956\times CRL$
BPD	Log (GA)=1.4768+0.008757×BPD+0.2803×log (BPD)
HC	$\log_e(GA)=0.010611\times HC-0.000030321\times HC^2+0.43498\times 10^{-7}HC^3+1.848$
AC	$GA=7.61+0.07645\times AC+0.0000393\times AC^2$
FL	$\log_e(GA)=0.034375\times FL-0.0037254\times FL\times\log_e(FL)+2.306$
EFW	GA=10.85+0.0006*HC*FL+0.067*BPD+0.0168*AC

[Table/Fig-1]: Biometry regression formulas.
CRL: Crown rump length; BPD: Biparietal diameter; HC: Head circumference; AC: Abdominal circumfrence; FL: Femur length; EFW: Estimated fetal weight; GA: Gestational age; All measurements are taken in mm

The pregnancies were followed up till delivery. The number of subjects with pre-eclampsia and SGA were noted. We defined pre-eclampsia as new onset hypertension (systolic BP >140 mmHg and diastolic BP >90 mmHg), after 20 weeks of gestation in association with proteinuria (either 1+protein on urine dipstick test or excretion of 300 mg of protein in 24 hours period [10,11]. The birth weight was recorded using calibrated electronic weighing scale to the nearest decimal in grams. The GA was re-estimated by neonatologist based on physical and neurological examination of the newborn. Both GA and birth weight was plotted on the standard GA specific birth weight centile chart and the neonate was labeled as "SGA" if its weight fell below 10th centile.

STATISTICAL ANALYSIS

The SPSS software (version 16.0, Chicago Il, USA) was used. The means and standard deviations were calculated using descriptive analysis provided by the software. The normality of observed measurements was tested by Kolmogorov-Smirnov method and student t-test was used to determine the statistical differences between two means. Categorical variables were tested using Pearson's chi-square test (with Yate's correction). For each biometric parameter, the best cut-off for discrepancy value was determined along with their diagnostic ability in terms of sensitivity, specificity, positive and negative likelihood ratio with their 95% confidence intervals. The AUC and z-test statistics were taken into account to decide the best parameter to predict adverse outcome. A p-value of <0.05 was considered statistically significant.

RESULTS

The number of women analysed for adverse outcome were 314 at the end of study period. All of these had ultrasound examination as per study requirement i.e., both 11-14 week and 18-20 week scans. The study cohort did not essentially include pregnancies with major congenital malformations or intrauterine foetal demise as the part of protocol. Exclusively only two main outcome measures such as SGA and pre-eclampsia were studied.

Based on occurrence of SGA as defined as in section on materials and methods, these 314 patients were further divided into SGA (n=62) and AGA (n=252) group. The prevalence of SGA in present study was 62 (19.7%). There were no comparable differences between maternal age, parity, the final duration of pregnancy [Table/Fig-3]. However, the mean birth weight was significantly low in SGA group compared to AGA group (2.47 kg vs 2.3 kg, p<0.001), obviously because SGA group mainly comprised of small babies as per requirement criteria.

There were no demonstrable differences between SGA and AGA group with regard to period of gestation at the time of delivery (37.2 week vs. 38.4 week, p=0.42) and none of the groups had any predilection for pre-eclampsia (8% vs. 9.5%, p=0.46). There were 13 patients who delivered before 37 weeks, giving preterm birth

Examples	First scan date and CRL value	First scan estimated GA according to CRL	Second scan date and biometric value	Actual GA based on CRL at the time of second scan	Estimated GA at the time of second scan	Biometric discrepancy at the time of second scan (in days)
Case A	22-02-2015, 52 mm	11 W 5 D	16-04-2015, BPD 43 mm	19 W 1 D	18 W 2 D	- 6
Case B	03-03-2015, 57 mm	12 W 1 D	20-04-2015, HC 168 mm	19 W 0 D	19 W 5 D	+ 5
Case C	06-04-2015, 55 mm	12 W 0 D	22-05-2015, AC 127 mm	18 W 4 D	18 W 1 D	- 3
Case D	26-06-2015, 49 mm	11 W 4 D	24-08-15, FL 32 mm	20 W 0 D	20 W 0 D	Nil (Zero)
Case E	03-09-2015, 64 mm	12 W 5 D	27-10-2015, BPD 50 mm, HC 170 mm, AC 150 mm, FL 30 mm	20 W 3 D	19 W 5 D	- 5

[Table/Fig-2]: Case illustrations.
CRL: Crown rump length; BPD: Biparietal diameter; HC: Head circumference; AC: Abdominal circumfrence; GA: Gestational age; W: Weeks; D: Days

Paramaters	All (n=314)	SGA (n=62)	AGA (n=252)	p-value
Mat. age (mean±SD)	26.2±3.8	25.3±3.5	26.8±3.7	0.56[a]
Gestational age at delivery (mean±SD)	38.4±2.3	37.2±2.1	38.4±2.4	0.42[a]
Mean birth weight in grams (mean±SD)	2881±324	2476±143	2932±343	0.003[a]
Pre-eclampsia	30 (9.5%)	5 (8%)	25 (9.5%)	0.46[b]
Parity, n (%)				
Primiparae	141 (44.9%)	34 (54.8%)	107 (42.5%)	0.08[b]
Multiparae	173 (55.1%)	28 (45.2%)	145 (57.5%)	

[Table/Fig-3]: Demographic characteristics.
[a]Student t-test, [b]χ^2 test; SGA: Small for gestational age; AGA: Appropriate for gestational age; Mat: Maternal

rate of 4.1%. 22 neonates (7%) required admission to the neonatal intensive care unit.

The [Table/Fig-4] shows analysis of biometric discrepancies between SGA and AGA newborns. All parameters of SGA babies showed growth lag compared to AGA babies which was statistically significant (BPD p<0.001, HC p<0.001, AC p<0.001, FL p<0.01, and EFW p<0.001). The f-test for analysis of variances indicated that HC discrepancy had the highest pick up rate compared to all other parameters (f=86.1).

Parameter	SGA (n=62)		AGA (n=252)		Statistics	
	Mean±SD	95% CI	Mean±SD	95% CI	f	Signifi-cance
BPD discrepancy	-4.23±1.63	(-4.68 to -3.78)	-2.42±1.87	(-2.65 to -2.2)	42.1	<0.001
HC discrepancy	-4.13±1.77	(-4.63 to -3.64)	-2.05±1.41	(-2.23 to -1.88)	86.1	<0.001
AC discrepancy	-2.94±1.47	(-3.35 to -2.53)	-1.84±1.17	(-1.98 to -1.7)	35.3	<0.001
FL discrepancy	-2.63±1.43	(-3.03 to -2.24)	-1.91±1.11	(-2.05 to -1.78)	16.7	<0.01
EFW discrepancy	-4.56±1.87	(-5.08 to -4.04)	-2.75±2.16	(-3.01 to -2.49)	31.7	<0.001

[Table/Fig-4]: Relationships between biometric discrepancies and small for gestational age neonates.
BPD: Biparietal diameter; HC: Head circumference; AC: Abdominal circumfrence; FL: Femur length; EFW: Estimated fetal weight; GA: Gestational age; CI: Confidence interval

Using ROC analysis, we found the best cut-off value of biometric lag in days for each parameter [Table/Fig-5]. According to z-test values, again a lag of more than 3.5 days in HC growth was associated with highest specificity, meaning that in 86.3% of cases growth delay was absent. The highest sensitivity was observed for BPD, where in 77% of foetuses exhibited growth lag of more than 3.5 days. However, one should remember that ROC analysis is not for one single cut point; one can increase or decrease the value of cut-off to increase the sensitivity of the test, but at the cost of reduction in specificity. We have tried to fix the cut points at the values which indicated the maximum sensitivity and specificity as far as possible. When multiple biometric parameters are compared, it can be found that HC curve supersedes all the other parameters {AUC 0.815 (95% CI, 0.767 to 0.856), p-value <0.001}.

The incidence of pre-eclampsia in the present series was 30(9.5%). None of parameters except FL were able to detect onset of pre-eclampsia [Table/Fig-6]. Though, p-value for FL was 0.02, the difference in FL delay in pre-eclampsia and normotensive groups was only 0.55 days and hence, utility of FL delay is questionable in predicting pre-eclampsia.

Parameter	Pre-eclampsia (n=30)		Normotensive (n=284)		Statistics	
	Mean±SD	95% CI	Mean±SD	95% CI	f	Signifi-cance
BPD discrepancy	-2.67±2.25	(-3.51 to -1.83)	-2.73±1.92	(-2.95 to -2.5)	0.03	0.87
HC discrepancy	-2.73±2	(-3.48 to -1.99)	-2.36±1.63	(-2.55 to -2.17)	1.34	0.25
AC discrepancy	-2.27±1.41	(-2.79 to -1.74)	-2±1.27	(-2.15 to -1.85)	1.2	0.28
FL discrepancy	-2.53±1.25	(-3 to -2.07)	-1.98±1.18	(-2.12 to -1.84)	5.95	0.02
EFW discrepancy	-3±2.41	(-3.9 to -2.1)	-3.06±2.2	(-3.31 to -2.8)	0.02	0.89

[Table/Fig-6]: Relationship between biometric discrepancies and pre-eclampsia.
BPD: Biparietal diameter; HC: Head circumference; AC: Abdominal circumfrence; FL: Femur length; EFW: Estimated fetal weight; GA: Gestational age; CI: Confidence interval

DISCUSSION

Earlier it was thought that factors that result in birth of SGA foetuses mainly operate in the latter half of the pregnancy as nutrient requirements for the developing embryo is minimal in the early part of the pregnancy. The result of the present study emphasises that SGA babies may have their origin in the early part of the pregnancy as evidenced by biometric lags of ultrasonologically derived parameters. In one of the studies, small first trimester CRL (with a lag of two to six days) resulted in delivery of increased number of low birth weight babies and preterm delivery [23]. Thus, screening models which incorporate first trimester growth discrepancies may predict growth abnormalities better compared to other available models, for example; first trimester serum markers, uterine artery doppler in the second trimester, or combined markers which include serum biochemistry, doppler and maternal characteristics [24-26].

At present it is difficult to predict which foetuses are likely to develop complications at the beginning of pregnancy. Defective placentation may be one of the causes of SGA later in pregnancy. It may be also associated with poor waves of trophoblastic invasion of spiral arteries, which again is one of the risk factors for development of pre-eclampsia and associated adverse pregnancy outcomes [27,28]. Use of extensive ultrasound monitoring of foetal growth has enabled prompt detection of foetal growth restriction, however, available evidences suggest that more than third of SGA babies are not identified till delivery [29]. This may be because some of these foetuses who has early trimester lag may achieve faster growth velocity towards third trimester of pregnancy [30]. However, still these foetuses may develop neonatal complications and hence, need recognisation earlier in the pregnancy. By studying the biometric growth lags, one may be able to identify them and keep a close watch by incorporating various methods of foetal surveilliance tests and can avoid potential intrauterine death. Surveilliance also includes regular uterine artery doppler to predict adverse obstetric

Parameter	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	+LR (95% CI)	-LR (95% CI)	Under the ROC curve (AUC)	z statistic	p-value
BPD	>3.5	76.92 (63.2-87.5)	72.14 (66.3-77.5)	2.76 (2.3-3.3)	0.32 (0.2-0.5)	0.77 (0.719 to 0.815)	6.709	<0.001
HC	>3.5	67.31 (52.9-79.7)	86.26 (81.5-90.2)	4.9 (4.0-6.0)	0.38 (0.2-0.6)	0.815 (0.767 to 0.856)	8.417	<0.001
AC	>2	71.15 (56.9-82.9)	58.02 (51.8-64.1)	1.69 (1.4-2.1)	0.5 (0.3-0.8)	0.713 (0.660 to 0.763)	5.003	<0.001
FL	>2.5	59.62 (45.1-73.0)	72.9 (67.1-78.2)	2.2 (1.7-2.8)	0.55 (0.4-0.8)	0.671 (0.616 to 0.723)	3.898	<0.001
EFW	>2.5	59.62 (45.1-73.0)	72.9 (67.1-78.2)	2.2 (1.7-2.8)	0.55 (0.4-0.8)	0.732 (0.680 to 0.781)	5.548	<0.001

[Table/Fig-5]: ROC test characteristics for various biometric discrepancies as predictors for small for gestational age.
BPD: Biparietal diameter; HC: Head circumference; AC: Abdominal circumfrence; FL: Femur length; EFW: Estimated fetal weight; AUC: Area under curve; ROC: Receiver operator characteristic

outcomes such as occurrence of pre-eclampsia and interventions such as aspirin therapy, treatment of hypertension may reduce the severity of such complications.

Many have investigated the potential use of BPD measurements to predict adverse foetal growth [2,31,32]. Simic M et al., from Sweden studied, 69,550 singleton pregnancies and correlated first trimester CRL scans with early mid trimester foetal biometry [32].

They applied z-score statistics to identify those foetuses which exhibited slow BPD growth. Adjusted Odds Ratio (aOR) for interval growth of BPD less than 2.5 percentile indicated elevated risk of SGA babies by 1.67 times and this risk was independent of causative factors for SGA such as pre-eclampsia and hypertensive diseases. Another way to look at BPD discrepancy is estimation of biometric lag as in the present study, which too demonstrated similar findings.

It is well known that AC less than 5th centile in the third trimester of pregnancy predicts compromised foetal circulation in the sense that cerebral circulation is maintained at the cost of reduced splanchnic circulation. A raised FL/AC ratio also may suggest cardiovascular changes that occur in foetal growth restriction. However, role of early AC and FL discrepancy has not been studied extensively. Schwartz N et al., from Philadelphia studied, extensively early biometric lag and adverse obstetric and perinatal outcome. They found that birth of SGA baby was associated with significant growth lags of various biometric parameters estimated during second trimester targeted scans. These lags included BPD lag (p=0.055), HC lag (p=0.017), AC lag (p=0.001) and EFW lag (p=0.007) and AC lag (p=0.001) during their second trimester anatomic survey. However, they could not associate biometric growth lags and occurrence of pre-eclampsia [22]. In the present study too, none of parameters except FL were able to detect onset of pre-eclampsia. Though, p-value for FL appeared to be significant (p=0.02), there was a delay of only 0.55 days pre-eclampsia and at present we can not definitely opine that biometric lags serve as predictor of pre-eclampsia. Similar opinion has been expressed by Pedersen NG et al., [31].

Another study by Tuuli MG et al., examined the value of EFW at 18-22 weeks of gestation in predicting SGA foetuses among 8978 singleton pregnancies [33]. They used z-scores cut-offs to associate SGA outcome with growth profiles. EFW z-score less than -1.0 was found to be associated significantly with growth restriction (aOR 3.44, 95% CI, 2.85-4.15) with sensitivity and specificity of 37.2% and 85.5%, respectively. They opined that there is a definite association between early growth restriction and adverse perinatal outocome.

We definitely know that placental malfunction is the starting point for intrauterine growth restriction. Till today there is no single novel marker which can detect these complications right from the first trimester of pregnancy. The present study potentially may reflect the role of early growth discrepancy in anticipating these problems.

LIMITATION

Though, we were able to demonstrate correlation between early foetal growth discrepancies and occurrence of SGA foetues, we could not demonstrate the same association in relation to pre-eclampsia. This may be because the sample size of SGA foetuses was larger than pre-eclampsia group (62 vs. 30) among patients. This is due to the fact that prevalence of SGA is more than that of pre-eclampsia in general obstetric population at any given time. Therefore, it is presumable that even one can find significant association between pre-eclampsia and early pregnancy growth delay by simply conducting the study on a large population.

CONCLUSION

The present study demonstrates that there is clear cut evidence between early growth discrepancies and occurrence of SGA foetuses. This implies a need for up gradation of ultrasound software which takes into account of first trimester growth as a starting point and calculates automatically the growth delay at time of second trimester targeted anomaly scan, thereby problematic pregnancies can be picked up early and necessary modifications and interventions can be made well in advance before irreversible damage may already have occurred.

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